required, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

IN THE CLAIMS:

Please amend Claim 3 to read as follows:

3. (Twice amended) The assay of Claim 2 in which the host cell protein is nucleoprotein interactor-1.

REMARKS

Applicants note with appreciation that the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of written description support has been withdrawn. Claims 2-8, 11, 12, 14-17, and 57-74 are pending in the instant application. Applicants have amended Claim 3 to correct a typographical error. A marked up version of the claims amended herein, with the deletion and addition indicated by brackets and underlining, respectively, is attached hereto as Exhibit A. A copy of the claims that will be pending upon entry of this Amendment is attached hereto as Exhibit B. The amendment to Claim 3 does not constitute new subject matter.

The remarks and amendment made herein narrow the issues on appeal and are designed to place the application into condition for allowance. As such, Applicants respectfully request that the remarks and amendment made herein be entered and fully considered.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claims 2-8, 11, 12, 14-17, and 57-74 are rejected under 35 U.S.C. §112, first paragraph, as not enabled by the specification. The Examiner contends that the claims are excessive in breadth and that the specification fails to provide sufficient guidance to enable one skilled in the art to practice the claimed invention. In particular, the Examiner contends that the specification fails to provide: (1) sufficient guidance regarding host cell proteins that are capable of binding specifically to influenza virus nucleoprotein (NP); (2) sufficient guidance regarding the molecular determinants modulating the specific binding interactions between host cell proteins and influenza virus NP; (3) sufficient guidance regarding host cell proteins and fragments thereof, as well as fragments of influenza virus NP, that will function

in the recited screening assays; and (4) a sufficient number of working embodiments. For the reasons detailed below, Applicants respectfully assert that the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement cannot stand and should be withdrawn.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation from the disclosure in the patent specification coupled with the information known in the art at the time the application was filed. *U.S. v. Telectronics, Inc.* 857 F. 2d 778, U.S.P.Q.2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F. 2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). The court of Appeals for the Federal Circuit has determined that experimentation, though laborious, is not undue experimentation where the specification provides a reasonable amount of guidance. *In re Wands*, 858 F. 2d 731 (Fed. Cir. 1988). In the present instance, the specification provides one of ordinary skill in the art with sufficient guidance to meet the requirements of Section 112.

Contrary to the Examiner's contention and as argued in the response filed by the Applicants on December 20, 2001 ("the December 20th response"), the specification does, indeed, provide sufficient guidance to one of skill in the art to identify host cell proteins that interact with the influenza virus nucleoprotein (NP) and to identify substances that inhibit that interaction. The specification describes six host cell proteins, nucleoprotein interactor ("NPI")-1, NPI-2, NPI-3, NPI-4, NPI-5, and NPI-6, that interact with the influenza virus NP. For clarity of discussion, the specification provides particular detail regarding the isolation and characterization of NPI-1, and its interaction with the influenza virus NP protein (*see* the specification of the present application at page 8, *ll.* 9-26; Example 6 at page 34, line 1 to page 44, line 2). However, as stated in the specification on page 8, ll. 22-26, the principles may be analogously applied to the identification and characterization of other host cell proteins that interact with influenza virus NP or other influenza viral proteins. In the case of NPI-1, the complete nucleotide sequence of the cDNA and the protein encoded by it are provided and biochemical characterization assays are presented that have assessed the interaction with influenza virus NP (*see* the specification of the present at page 11, line 1 to page 13, line 35). Moreover, the specification of the present application provides guidance to enable one skilled on the art to identify other host cell proteins that interact with influenza virus NP which can be employed in the assays of the claimed invention (*see* the specification of the present invention at page 9, *ll.* 11-29). In particular, the specification of the present application provides the yeast interactive trap system as an exemplary assay for identifying

the interaction of host cell proteins with the viral proteins. This assay as well as other analogous assays for identifying protein-protein interactions were well-known in the art as of the effective filing date of the present application (*see, e.g.*, Gyuris *et al.*, 1993 *Cell* 75: 791-803; Zervos *et al.*, 1993, *Cell* 72: 222-32 attached hereto as Exhibit C). Thus, Applicants respectfully assert that the specification does provide sufficient guidance to identify host cell proteins that are capable of interacting with influenza virus nucleoprotein.

Additionally, Applicants would like to respectfully remind the Examiner, that while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed the Court of Custom and Patent Appeals in *In re Angstadt* 536 F.2d, 190 USPQ 214 (CCPA 1976) has explicitly cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue. Applicants respectfully assert that the specification provides sufficient guidance to one skilled in the art to practice the claimed invention, *e.g.*, screen and identify host cell proteins that interact with viral proteins needed for viral replication, without undue experimentation.

The Examiner additionally contends that the host cell proteins identified as nucleoprotein interacting proteins "do not share any common structural features," and that to date none of the proteins identified share any genetic relatedness. Applicants respectfully assert that the instant specification does not provide an absolute requirement that the host cell proteins identified as influenza virus NP interacting proteins share a common structural feature, and it thus appears that the Examiner has erroneously imposed this requirement on the claimed invention. Although the host cell proteins identified as influenza virus nucleoprotein interacting proteins could have genetic homology as indicated in the instant specification, *see, e.g.*, page 17, *ll.* 14-35, this is by no means a requirement for all the host cell proteins identified as influenza virus NP interacting proteins. Accordingly, the host cell proteins identified as nucleoprotein interacting proteins need not be genetically homologous. The absence of genetic relatedness by no means precludes the identification of the nucleoprotein interacting proteins. Additionally, Applicants respectfully invite the Examiner's attention to the post-filing date paper by Wang *et al.* (1996, *J. of Virology*, 71(3): 1850-6 ("Wang"); attached hereto as Exhibit D). Wang discloses mutagenesis studies in which the molecular features of NPI-1 and NPI-3 are assessed and NPI-1 and NPI-3 are identified as both belonging to the Karyophorein-a/importin 60 protein family. Thus, contrary to the Examiner's contention, at least two of the nucleoprotein interacting proteins disclosed in the instant specification share structural homology.

The Examiner further alleges that the "mere finding that two proteins interact with one another does not mean that the binding interaction is meaningful in the context of a viral infection" (page 3 of the Office Action, paper no. 30). The specification provides *in vitro* methods for identification of binding interactions between host cell proteins and viral protein needed for viral replication and also provides guidance to one skilled in the art for further assessing the binding interaction in an *in vivo* and/or animal model. The specification provides viral replication assays, *e.g.*, hemagglutination assays and animal model assays, for characterizing the host cell proteins identified (*see* instant specification at page 28, line 3 to page 29, line 7). Additionally, viral replication assays were known and routine to one skilled in the field of virology at the time of filing of the instant specification. Therefore, the specification coupled with the information known as of the effective filing date of the instant application would have enabled one of skill in the art to identify and characterize host cell proteins that interact with viral proteins needed for viral replication which could be employed in the claimed invention.

Applicants respectfully assert that contrary to the Examiner's contention, the specification provides ample guidance to one skilled in the art regarding methods for the identification of fragments from either the viral or the cellular protein (*see*, *e.g.*, the instant specification at page 20, line 11 to page 21, line 3) for use in the methods of the invention. In fact, as the Examiner also points out the specification describes a peptide fragment of the host cell protein NPI-1 comprising amino acids 262-526 that binds to the influenza virus nucleoprotein. Additionally, techniques for mapping protein-protein interaction and determining the molecular determinants for modulating the interactions of binding partners (*e.g.*, mutagenesis such as alanine scanning mutagenesis) were well-known and routine for one skilled in the art as of the filing date of the instant specification. Thus, the specification coupled with the information known as of the effective filing date of the instant application would have enabled one of skill in the art to ascertain the amino acid residues of a viral protein, *e.g.*, influenza NP, required for interaction with a host cell protein, *e.g.*, nucleoprotein interacting protein, without undue experimentation.

In view of the foregoing, Applicants submit that the invention as claimed is fully enabled by the specification of the instant application. Accordingly, Applicants respectfully assert that the rejection under 35 U.S.C. §112, first paragraph, cannot stand and should be withdrawn.

CONCLUSION

Applicants believe that the present claims meet all of the requirements for patentability. Entry and consideration of the foregoing amendment and remarks into the file of the above-identified application is respectfully requested. Withdrawal of all the rejections and reconsideration of the claims is requested.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-6431.

Respectfully submitted,

Date: April 24, 2003

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